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# Cardiogenic Shock in the Canadian Landscape: Key Concepts for the Practicing Clinician

**Jordan D. Gibson, MD, FRCPC**
**Ayaaz K. Sachedina, MD, FRCPC**

## Introduction

Cardiogenic shock (CS) is generally defined as a state of end-organ hypoperfusion secondary to an inability of the heart to deliver sufficient oxygenated blood to the tissues.[1] Although CS is often initiated by an event that specifically affects the cardiovascular system, without prompt intervention, it can lead to a cascade of insults on other organ systems that result in additional morbidity and mortality. Despite advances in temporary mechanical circulatory support (MCS) technology over the past 2 decades, studies have consistently reported a 30% to 50% mortality rate for patients with CS at 6 to 12 months, though this rate may exceed 70% depending on the severity of the shock and individual patient factors.[2] This review will provide an overview of key concepts in CS including current definitions, hemodynamic assessment, shock state classifications, and prognostication.

## Etiology of Cardiogenic Shock

In contemporary cardiac intensive care units, several conditions can lead to CS. Acute myocardial infarction (AMI), complicated by CS (AMICS), accounts for approximately 30% of shock cases, while the incidence of CS complicating AMI has been reported to be between 7% to 10%.[3] Non-ischemic cardiomyopathies are responsible for 28% of cases, ischemia without AMI comprises 18%, and various other causes (valve dysfunction, arrhythmia, among others) are responsible for 17%. The remaining 7% of cases are reported as unknown or missing.[4]

## Definitions of Cardiogenic Shock

CS is a clinical diagnosis, however, criteria have been proposed to standardize its definition.

**The landmark SHOCK trial defined CS based on 3 variables:**

1. Hypotension (a systolic blood pressure of <90 mm Hg for at least 30 minutes or the need for supportive measures to maintain a systolic blood pressure of >90 mm Hg
2. Evidence of end-organ hypoperfusion (cool extremities or a urine output of <30 mL per hour)
3. Impaired cardiac hemodynamics, defined as a cardiac index (CI) of less than 2.2 litres per minute per square metre of body-surface area, and a pulmonary artery wedge pressure (PAWP) of at least 15 mm Hg.[3]

Although subsequent studies have introduced slight variations to these criteria, the overall concepts have remained consistent. Definitions of hypoperfusion have been broadened to include an elevated arterial lactate level (>2 mmol/L), acute kidney injury (creatinine ≥2 times the upper limit of normal), acute hepatic injury (ALT >3 times the upper limit of normal), cool or mottled extremities, or altered mental status not explained by an alternate cause. Similarly, hemodynamic criteria have been broadened to include a systemic vascular resistance index (SVRI) >2200 dynes/(cm·sec-5).[2]

## Key Hemodynamic Indices in Cardiogenic Shock

The altered hemodynamics in CS are often best assessed by right heart catheterization. This procedure can provide critical information in the initial assessment of CS and in monitoring the response to therapy. In addition to the indices

| Hemodynamic Index | Formula | Normal Value |
|---|---|---|
| CPO | $\frac{(Cardiac\ output)(Mean\ arterial\ pressure)}{451}$ | >0.6 Watts[5] |
| PAPi | $\frac{(PASP - PADP)}{RAP}$ | >1.85[33] |
| RVSWi | $(mPAP - RAP)(SVi)(0.0136)$ | 8-12 g/m/beat/m$^{2}$[,34] |
| RAP:PAWP | $\frac{RAP}{PAWP}$ | 0.43-0.75[35] |

**Table 1.** Key hemodynamic indices in shock evaluation; *courtesy of Ayaaz K. Sachedina, MD, FRCPC and Jordan D. Gibson, MD, FRCPC*

**Abbreviations: CPO:** cardiac power output, **mPAP:** mean pulmonary artery pressure, **PADP:** pulmonary artery diastolic pressure, **PAWP:** pulmonary artery wedge pressure, **PASP:** pulmonary artery systolic pressure, **PAPi:** pulmonary artery pulsatility index, **RAP:** right atrial pressure, **RVSWi:** right ventricular stroke work index, **SVi:** stroke volume index

mentioned above for defining CS, other important parameters include cardiac power output (CPO), pulmonary artery pulsatility index (PAPi), and right atrial to pulmonary artery wedge pressure ratio (RA:PAWP) **(Table 1)**.

CPO is a measure that considers both cardiac output and the ability of the heart to generate systemic flow and blood pressure. A CPO cutoff of less than 0.6 W has been shown to have the best sensitivity and specificity for predicting worsening heart failure in patients admitted with CS.[5]

In addition to assessing left ventricular (LV) function and filling pressures, right heart catheterization is a powerful tool for assessing right ventricular (RV) function. The PAPi is used to assess right heart function, with lower values suggesting right heart dysfunction.[6] Multiple studies have shown an increase in adverse outcomes, including all-cause mortality, in a variety of patient populations with a low PAPi.[6–8] Although there is no universally agreed upon PAPi value to identify "high-risk" individuals, a recent study found that hospitalized patients in the lowest 3 quartiles undergoing right heart catheterization had increased mortality compared with those in the highest PAPi quartile, suggesting that PAPi may play a role in modelling risk across a range of cardiac presentations. Other helpful RV hemodynamic indices include the RA:PAWP and the right ventricular stroke work index (RVSWi) **(Table 1)**. An elevated RA:PAWP value is also associated with right heart dysfunction. While an elevated RA:PAWP appears to be associated with an increase in mortality, the RVSWi may be less predictive of outcomes than the PAPi and RA:PAWP.[6]

Finally, while not widely used in clinical practice for prognosticating shock, evidence suggests that microvascular perfusion parameters may be associated with adverse outcomes in CS.[9,10] This topic is the subject of much ongoing research and holds promise for improving prognostication and serving as a potential future therapeutic target.

Appropriate hemodynamic assessment and identification of impaired cardiac function with univentricular or biventricular involvement is imperative for determining the appropriate treatment strategies. Selecting a specific medical therapy and MCS strategy that is directed to the area and degree of cardiac impairment facilitates more effective and supportive intervention.

## Classification of Cardiogenic Shock

A key concept in the management and ongoing research of CS is its inherent heterogeneity, both in severity and underlying etiology. The most widely used classification in contemporary practice and research is The Society for Cardiovascular Angiography and Interventions (SCAI) classification of shock. This scheme **(Figure 1)** was first proposed in 2019 in an effort to improve upon the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) definition.[11] The SCAI shock classification is an ordinal scale that grades shock severity from A (at risk of CS) through to E

(in extremis). Numerous validation studies have shown that the SCAI classification consistently predicts increasing mortality from grades B to E.[12–14]

While the SCAI classification has been helpful for standardizing and stratifying shock severity, providing a more consistent description of patient populations in both clinical practice and research, limitations have been described.[15] These limitations include the lack of discrimination of shock severity from stages C to D, the lack of discrimination between LV, RV, and biventricular failure, and the absence of therapeutic guidance based on clinical presentation. An updated SCAI classification was recently proposed that incorporated additional modifiers into the SCAI shock classification to address these limitations.[16] In this scheme, it was suggested that SCAI stage C be further stratified as follows: hypoperfusion with normal blood pressure, hypoperfusion with hypotension or 1 vasopressor, or hypoperfusion with hypotension and >1 vasopressor. Within each strata, it was further suggested to add a modifier to identify LV failure, RV failure, or biventricular failure. For defining SCAI stages D and E, specific cutoffs are also suggested for lactate levels and for the number of vasopressors to add granularity, thereby defining these as discrete states on a continuum of CS severity.[15]

The etiology of CS contributes another layer of heterogeneity to this patient population. The Shock Academic Research Consortium (SHARC) recently proposed a framework for classifying the underlying causes of CS, which will improve discrimination of CS phenotypes in future research studies **(Figure 1)**. They suggested classifying shock into several types: acute myocardial infarction-related CS (AMI-CS) with or without ST-segment elevation; heart failure-related CS (HF-CS), which can be further classified as de novo or acute-on-chronic; secondary CS (from another, non-myocardial cause); and post-cardiotomy CS (in the setting of cardiac surgery), which can be further classified by surgery type. In the future, machine learning approaches may also play a role in further stratifying phenotypes of CS.[17]

## Prognosis and Outcomes of CS States

The SCAI shock classification has been shown to be a helpful prognosticator of mortality during the initial assessments and reassessments of patients with CS. Early validation studies of the SCAI shock classification reported in hospital or 30-day mortality rates of 33.9% for SCAI B, 10.7-53.9% for SCAI C, 24-66.9% for SCAI D, and 42.0-77.4% for SCAI E, respectively.[12,18–20] In recent years, there has been a focus on the utility of conducting serial assessments of the SCAI shock classification. This approach recognizes the dynamic trajectory of patients with CS, however, most early validation studies assigned a shock class at the time of admission. In a recent study,

| | | | |
|---|---|---|---|
| **A** | At risk for CS without signs or symptoms | **AMI-CS** | Shock in the setting of ACS (may be NSTEMI or STEMI). |
| **B** | Hypotension and/or tachycardia without hypoperfusion | | |
| **C** | Hypoperfusion requiring pharmacologic or mechanical support | **HF-CS** | Shock secondary to right, left or biventricular failure in the absence of ACS. May be de novo or acute on chronic. |
| **D** | Clinical condition worsening despite efforts to support | **Secondary CS** | Due to another non-myocardial cardiac cause (arrhythmic or valve disease). |
| **E** | Patient in extremis and may have ongoing CPR | **Post-cardiotomy CS** | Following cardiac surgery. |

**Figure 1.** Classification of cardiogenic shock. a) SCAI classification of CS severity b) SHARC classification of CS phenotypes; *courtesy of Ayaaz K. Sachedina, MD, FRCPC and Jordan D. Gibson, MD, FRCPC*

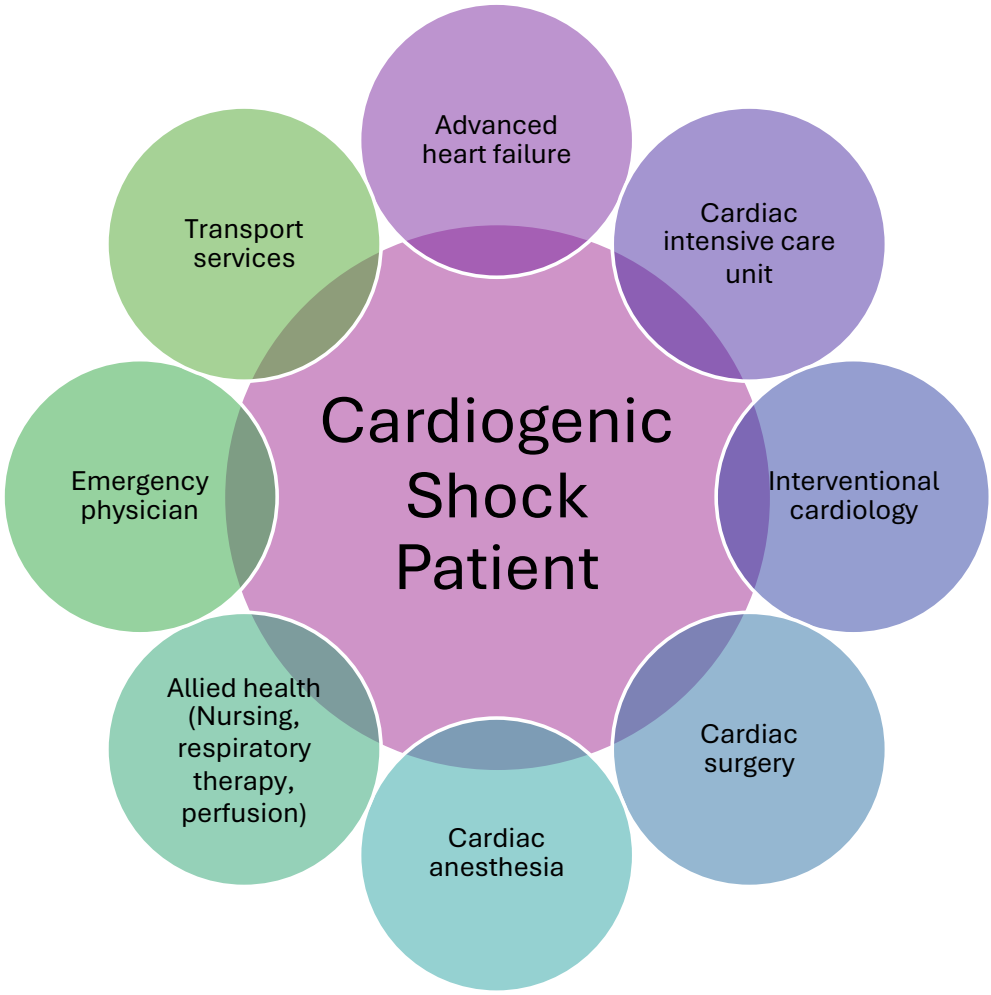


**Figure 2.** Multidisciplinary team required for management of a patient with cardiogenic shock; *courtesy of Ayaaz K. Sachedina, MD, FRCPC and Jordan D. Gibson, MD, FRCPC*

retrospectively assessing shock severity every 4 hours over the first day of a cardiac intensive care unit admission in a population with and without shock, improved the prognostication accuracy.[21] It has also been shown that a single re-evaluation of the SCAI classification at 24 hours, whether it is improving or worsening, along with the maximum SCAI class assigned over a patient's course, offers additional prognostic information.[22–24]

The long-term outcomes amongst survivors of CS are highly variable. While some patients recover with minimal support, a recent report using data from the United States National Inpatient Sample of 332120 patients identified with CS, 5710 (1.7%) went on to receive an LV assist device, or cardiac transplant during their index admission.[25] An awareness and understanding of these possible trajectories is essential in managing patients with CS. The early involvement of advanced heart failure specialists in the care of patients with CS can help identify those who are not showing signs of independent recovery and optimize their candidacy for long-term advanced therapies or transplant.

## The Role of Shock Teams

The first 24 hours following a patient's admission for CS are critical for their outcome. Early activation of multidisciplinary specialists through shock team models has been shown to improve outcomes in CS **(Figure 2)**.[26,27] Leveraging the expertise of a diverse group of specialists facilitates the optimization and standardization of clinical practices, which historically have varied

amongst different centres depending on the volume of CS that they treat.[28]

Involving clinicians with different areas of expertise early in the management of a patient, and facilitating their transfer to a specialized cardiac centre, can improve outcomes. Several studies have independently shown improvements in patient survival with the involvement of a CS team.[26,28] The involvement of CS teams can also facilitate the earlier deployment of advanced MCS and increase the use of pulmonary artery catheters. This approach helps to better identify the etiology of a patient's shock state and guide subsequent treatment. Given the heterogeneity of CS, it is important to recognize that a "one-size-fits-all" approach to it does not exist and that future research should strive to consider shock phenotypes when assessing responses to specific therapies.[29,30] While many advanced MCS options are available to support patients with CS, there is no evidence to date that suggests the superiority of one device over another, or over medical management, in all-comers with CS. However, when treatment strategies are guided by the patient's etiology and degree of hemodynamic impairment, there is a greater potential for more effective and directed therapy. Earlier involvement of a CS team during the patient's management course can help with these decisions.

## Unique Features of Cardiogenic Shock Management in Canada

In Canada, the delivery of CS care has unique features, particularly when comparing it to care in the United States. Firstly, the geographic and per capita density of centres capable of offering advanced therapies and transplants is relatively low.[31,32] In Canada, there are 9 centres that offer the full spectrum of care for CS patients, including cardiac transplant.[31] Thus, access to advanced cardiac centres with full MCS options and heart transplant services can be challenging due to the limited number of centres offering these services and the large catchment areas for each centre.[31]

In Canada, there is also significant variability of mechanical support options available by centre. A recent survey of all Canadian centres with cardiac catheterization and revascularization capabilities (N=46) reported that intra-aortic balloon pumps (IABP) were available at all centres, however, percutaneous LV assist devices were available at only 39.1%, and extracorporeal membrane oxygenation (ECMO) was available at 65.2%. In a forthcoming report comparing shock management and outcomes between Canada and the United States, the use of pulmonary artery catheters and Impellas was significantly higher in the United States compared to Canada. The adjusted mortality for patients presenting with CS was also reported to be lower in the United States compared to Canada (29.4% vs 37.1%, $p = 0.0004$)[36]. Exploring and addressing the reasons for these differences will be important for future research.

## Conclusion

Despite advancements in Cardiology over recent decades, mortality rates for CS remain high in Canada and globally. CS is a heterogeneous condition, and its management is further complicated by the unique and diverse treatment settings within the Canadian landscape of cardiovascular care. Moving forward, hospital centres will require ongoing efforts to define pathways to ensure prompt initiation and ongoing discussion of care for patients with CS. In addition, further evidence will be required to define the best therapeutic options for specific phenotypes of patients presenting with this heterogeneous condition.

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## Financial Disclosures

**A.S.:** None declared
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# The Importance of Hypertriglyceridemia: Risk of Atherosclerosis and Available Treatments

**Robert A. Hegele, MD, FRCPC, Cert Endo, FACP**

## Introduction

Serum triglycerides are derived from both exogenous and endogenous sources.[1] Exogenous triglycerides are obtained through the diet and circulate post prandially within large, intestinally-derived chylomicron particles, which are normally cleared within 3 to 4 hours after eating.[1] Endogenous triglycerides are hepatically produced and circulate in smaller very low density lipoprotein (VLDL) particles, which are remodelled in plasma to form even smaller triglyceride-depleted low density lipoprotein (LDL) particles.[1] While the atherogenic impact of LDL and its cholesterol content are well appreciated, the atherogenic role of triglyceride-rich lipoprotein particles, including VLDL and various remnant lipoprotein species, had only recently come into focus.

Approximately 25% of the population has mild-to-moderate hypertriglyceridemia, characterized by triglyceride levels ranging from 2 to 9.9 mmol/L, while approximately 1 in 500 has severe hypertriglyceridemia, defined as triglyceride levels >10 mmol/L.[2] Pathogenic DNA variants within the gene encoding the triglyceride clearing enzyme lipoprotein lipase (*LPL*) or one of its co-factors (*APOC2*, *APOA5*, *GPIHBP1* or *LMF1*) can cause severe hypertriglyceridemia, that presents in childhood.[2] Adults with milder forms of genetic predisposition in combination with secondary factors, can also express triglyceride levels this high.[3]

The risk to health of severe hypertriglyceridemia is acute pancreatitis, which is related to the pathological persistence of chylomicron particles. However, chylomicrons are not considered to increase the risk of atherosclerotic cardiovascular disease (ASCVD).[3] In contrast, the cholesterol carried within VLDL and remnant particles in patients with mild-to-moderate hypertriglyceridemia does increase ASCVD risk.[2,3] Therapies aimed at lowering LDL cholesterol, such as statins, ezetimibe, and inhibitors of proprotein convertase subtilisin kexin 9 (PCSK9) are relatively ineffective at reducing triglycerides.[2,3] Historically, agents such as fibrates, niacin derivatives, and omega-3 fatty acids have been used to reduce

triglyceride levels, but their efficacy varies, and they do not reduce the risk of either acute pancreatitis or ASCVD.[2,3]

## Secondary Causes of Hypertriglyceridemia

Many cases of adult-onset hypertriglyceridemia result from secondary causes, as summarized in **Table 1**. These factors or conditions either increase hepatic triglyceride production or impair the clearance of triglyceride-rich lipoproteins, or both.[1-3] Secondary factors associated with elevated triglyceride levels include lifestyle factors, a diverse list of medical conditions, and a wide range of medications. For patients with hypertriglyceridemia, it is important to mitigate secondary causes, including potentially controllable medical conditions and/or culprit medications for which metabolically neutral alternatives are available.[2,3]

## Severe Hypertriglyceridemia and Chylomicronemia Syndrome

Severely elevated triglycerides are related to the pathological presence of chylomicrons.[4] Often, there are no symptoms or physical findings, but when these are present, the condition is referred to as chylomicronemia syndrome.[5] Clinical features of chylomicronemia include failure to thrive in infants, eruptive xanthomas, lipemia retinalis, hepatosplenomegaly, recurrent abdominal pain, nausea and vomiting, and an increased risk of acute pancreatitis. Less common clinical features include intestinal bleeding, pallor, anemia, irritability, diarrhea, seizures, and encephalopathy. In children, severe hypertriglyceridemia and chylomicronemia syndrome can be genetically determined by autosomal recessive Mendelian inheritance and is referred to as "familial chylomicronemia syndrome" (FCS).[4] The causal genes for FCS can now be detected on DNA sequencing panels that are becoming more accessible clinically.[4] In adults, severe hypertriglyceridemia and chylomicronemia syndrome are multifactorial, with a complex contribution of polygenic predisposition plus a significant influence of the secondary factors mentioned above.[5] Genetic testing in adults with severe hypertriglyceridemia is usually non-informative and is not currently recommended.[3]

Triglyceride levels >10 mmol/L are a risk factor for acute pancreatitis, which can be life-threatening. Triglyceride elevation in this range requires assertive management including significant dietary fat restriction, cessation of alcohol, and correcting secondary factors, especially obesity and diabetes. Plasmapheresis or intravenous infusions of insulin or heparin are not recommended for treating severe hypertriglyceridemia. Two novel biological therapies, olezarsen and plozasiran, have been shown to effectively treat severe hypertriglyceridemia and reduce pancreatitis risk.[6-8] While adult patients with severe hypertriglyceridemia or chylomicronemia also have an increased ASCVD risk, it is relatively less significant than their pancreatitis risk.[5]

## Mild-to-moderate Hypertriglyceridemia and ASCVD Risk

The more pertinent concern in cardiology is common mild-to-moderate hypertriglyceridemia, defined as triglyceride levels between 2 and 9.9 mmol/L, but typically <5 mmol/L.[2,3] These levels are observed in approximately 1 in 25 people, and while they are not associated with any physical findings, they are associated with an increased risk of atherosclerosis end points.[2,3] The link between elevated triglycerides and atherosclerosis is complex.[1] For instance, the atherogenic potential of liver-derived triglyceride-rich VLDL particles comes from their cholesterol content, which can be deposited within the arterial wall to form atherosclerotic plaques.[1] Furthermore, elevated triglycerides often co-exist with other adverse metabolic parameters, such as obesity, insulin resistance, hepatosteatosis, depressed high-density lipoprotein (HDL) cholesterol, and increased atherogenic small dense LDL particles, as well as a pro-coagulant and pro-inflammatory state.[2,3] All of these factors can amplify atherosclerosis risk.

For many years it was believed that triglycerides were not a direct cause of atherosclerosis and that their relationship with adverse cardiovascular outcomes was because triglycerides "kept bad company".[2,3] Today however, the balance of experimental evidence suggests that hypertriglyceridemia is itself an independent risk factor for ASCVD.[2,3] Several observational studies have demonstrated a graded association of elevated triglyceride levels with ASCVD risk, although this association is somewhat attenuated following adjustments for such confounders as obesity and insulin resistance. However, recent Mendelian randomization studies

— essentially genetic epidemiology studies in large populations — indicate that triglycerides play a direct causal role in atherosclerosis.[7] In contrast, previously suspected pathogenic factors such as reduced HDL cholesterol are now considered to be bystanders in the process.[7]

Mendelian randomization studies have linked genetic elevations in triglycerides to an increased risk of ASCVD outcomes, although there are some caveats inherent to these types of indirect studies that attempt to infer risk. For instance, studies of individuals with rare, large-effect loss-of-function variants in the APOC3 gene, which encodes apolipoprotein (apo) C-III have naturally low triglyceride levels and reduced rates of ASCVD compared to the general population.[7] However, these individuals also have reduced levels of LDL cholesterol, which could also be contributing to the reduced ASCVD risk.[7] Nonetheless, many researchers have speculated that new drugs which reduce apo C-III levels by targeting APOC3 mRNA, such as olezarsen and plozasiran,[8,9] might pharmacologically recapitulate the benefit seen in individuals with lower triglycerides by virtue of having been born with a natural genetic deficiency of the apo C-III protein.

In fact, the evidence of the benefit of lowering triglycerides pharmacologically with existing drugs to improve ASCVD outcomes is currently quite scarce. Most agents that lower triglycerides also affect other components of the lipid profile, making it a challenge to isolate the effect of triglyceride lowering alone from clinical trial data. For instance, a meta-analysis of 49 lipid trials was conducted and a multivariable meta-regression determined a relative risk of 0.84 (95% CI 0.75-0.94) per 1 mmol/L reduction in triglycerides, which was judged to be rather marginal and confounded by other variables, as mentioned above.[10] In contrast, the REDUCE-IT trial, a randomized trial of icosapent ethyl in high-risk individuals on statin therapy, showed that triglycerides were reduced by 20% with markedly improved ASCVD outcomes.[11]

## Treating Hypertriglyceridemia

### Lifestyle

Lifestyle interventions are recommended for all individuals with hypertriglyceridemia, since triglycerides are more responsive to lifestyle changes than other elevated lipoprotein levels, such as LDL cholesterol.[2,3] Weight loss, increasing physical activity, abstaining from alcohol, reducing simple sugar intake, and reducing intake of dietary trans and saturated fats can result in significant improvements in triglyceride levels.[2,3]

### Statins

Statins are highly effective at lowering LDL cholesterol but only moderately reduce triglycerides by 10-20%.[2,3] Statins also result in a qualitatively more favourable lipid profile, reducing triglyceride-rich remnant particles and shifting from small, dense particles to those that are larger and less atherogenic.[3] Despite these relatively marginal effects on triglyceride-rich lipoproteins, three decades worth of randomized clinical trials indicate that the majority of the benefit from statin therapy derives from their ability to reduce overall LDL cholesterol, which encompasses particles of all sizes.

### Niacin Derivatives

While niacin and its derivatives were popular in the late twentieth century for treating dyslipidemia, including hypertriglyceridemia, a series of neutral cardiovascular outcome trials combined with intolerability and an increased adverse effect profile[12] has essentially eliminated prescription niacin and related agents from the Canadian market.

### Fibrates

Fibrates are the currently available drug of choice for targeting severely elevated triglycerides in adults.[3,11] Fibrates act mainly through interacting with peroxisome proliferator activated receptor (PPAR)-alpha, which enhances fatty acid oxidation and suppresses fatty acid and triglyceride synthesis. They can lower plasma triglyceride levels by up to 60%.[3,13] Evidence from the late twentieth century suggests a cardiovascular benefit with fibrates as monotherapy and when used in combination with statins.[3,13] However, a recent randomized double-blinded clinical trial of pemafibrate added to statin therapy in patients with mild-to-moderate hypertriglyceridemia (triglyceride range 2 to 5.6 mmol/L) showed no benefit.[14] This has further dampened enthusiasm for fibrate therapy to reduce the risk of ASCVD in patients with mild-to-moderate hypertriglyceridemia who are already taking a statin. On the other hand, the use of fibrates in patients with severe hypertriglyceridemia is still considered valid by many lipidologists, with the rationale of reducing triglycerides below 10 mmol/L

in order to reduce the risk of acute pancreatitis.[2,3] However, no randomized clinical trial to date has shown that fibrates reduce the risk of pancreatitis.

## Omega-3-Fattty Acids

For years, researchers have been intrigued by the potential of fish oils, which have been linked epidemiologically to populations with a low ASCVD prevalence, such as circumpolar communities.[15] Fish oils are complex mixtures of various fatty acids. Omega-3 fatty acids, a family of fats found in fish oils, derive their name from the fact that the first double bond involves the third carbon from the methyl end. The main omega-3 fatty acid with cardiovascular benefit is eicosapentaenoic acid (EPA), named for its 5 double bonds along its 20-carbon backbone.[13]

The mechanism of action for triglyceride lowering with the use of omega-3 fatty acids is unclear, but they may act on multiple molecular targets to reduce triglyceride synthesis and secretion. Proposed mechanisms of action include suppressing the expression of sterol regulatory element-binding protein (SREBP)-1c, increasing the beta-oxidation of fatty acids, and inhibiting the enzymes involved in triglyceride synthesis. These agents may also enhance triglyceride clearance through increasing LPL activity.[16]

Omega-3-fatty acids have been used for years (with little effect) in the treatment of resistant hypertriglyceridemia; however, emerging evidence suggests that these agents may have additional cardiovascular benefits beyond triglyceride lowering. There is also debate regarding which formulation is most effective, and whether the preparation method that ensures minimal oxidation of omega-3 fatty acids is an important factor that influences their clinical effect.[16]

Both primary components of omega-3 fatty acids, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), effectively lower triglycerides. However, DHA has shown a greater triglyceride lowering ability and HDL cholesterol-raising capacity compared to EPA, but it also resulted in larger increases in LDL cholesterol compared to EPA.[14]

Studies using over-the-counter fish oils and omega-3 supplements have produced contradictory results, likely because studies are of variable quality and the laxness of regulations does not guarantee adequate quality or quantity of EPA in these supplements. Furthermore, some prescription forms of omega-3 fatty acids, available in the US but not in Canada, contain other types of fats that can neutralize EPA's benefits.[17]

The aforementioned REDUCE-IT trial was inspired by an earlier trial from Japan, the JELIS study, which showed a cardiovascular benefit of high dose pure EPA. In that study, 18,645 patients were randomly assigned to receive either 1.8 g EPA daily plus statin (N=9326) or statin alone (N=9319).[18] After 4.6 years, there were 262 major coronary events in EPA-treated patients compared to 324 events in controls, indicating that EPA reduced events by 19% (p=0.011). This suggested that high doses of pure EPA can prevent ASCVD.[18] Because EPA lowered plasma triglycerides, it was logical to focus on patients with mild-to-moderate hypertriglyceridemia when designing the REDUCE-IT trial.

The REDUCE-IT trial was a multinational study that randomized 8179 high-risk statin-treated patients to receive either 4 g of IPE daily or a placebo.[9] Among the participants, 58% had type 2 diabetes. The entry criteria included well-controlled LDL cholesterol (mean baseline level of 1.94 mmol/L) but elevated triglycerides between 1.5 and 5.6 mmol/L.[9] After 4.9 years, there was a 20% reduction in triglycerides and a 25% relative risk reduction in the composite primary end point, which included cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, revascularization procedures, and hospitalization for angina. The number needed to treat was 21 patients to prevent one event.[9] The composite outcome of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke was reduced by 26%, corresponding to a number needed to treat of 28.[9] Subsequent subgroup analyses of the REDUCE-IT trial have indicated that the cardiovascular benefits extend across a wide range of patients, largely irrespective of baseline demographics and clinical features. Because of the REDUCE-IT trial, IPE is recommended in the current Canadian Lipid Guidelines in the algorithm for the secondary prevention of ASCVD.[19]

## Apolipoprotein C-III (APOC3) Inhibitors

The development of inhibitors against apo C-III (designated hereafter as APOC3 inhibitors) has shown proven efficacy at lowering triglycerides across different patient populations. Two agents that target *APOC3* mRNA –olezarsen and plozasiran– are in advanced stages of development. Both olezarsen and plozasiran have

shown efficacy in Phase 3 clinical trials of patients with severe hypertriglyceridemia due to FCS or persistent chylomicronemia, reducing triglyceride levels by up to 80% and reducing pancreatitis risk by up to 88%.[8,9] Olezarsen (Tryngolza) received approval for this indication by the US Food and Drug Administration in late 2024, while approval for plozasiran for a similar indication is imminent. However, neither agent has been evaluated in clinical trials for patients with mild-to-moderate hypertriglyceridemia with the goal of reducing ASCVD risk. Therefore, while this mechanism and these agents are theoretically very attractive for cardiology, much work remains to validate them for reducing cardiovascular risk.

## How to Approach the Patient With Hypertriglyceridemia

The current approach to diagnosing, treating, and monitoring a patient with hypertriglyceridemia, with a focus on reducing ASCVD risk, is shown in **Figure 1**. In any adult with newly recognized hypertriglyceridemia, there are often contributing secondary causes **(Table 1)**. Addressing these secondary causes often goes a long way toward correcting the biochemical disturbance and should be the first-line management **(Figure 1)**.

For the patient with mild-to-moderate hypertriglyceridemia, the primary concern is the potential for excess ASCVD risk. It is important to manage ASCVD risk factors, such as hypertension, obesity, sedentary lifestyle, smoking, and diabetes concurrently. If pharmacological treatment is required, medications with proven cardiovascular benefit, such as statins, ezetimibe, and icosapent ethyl are preferred initially. Despite the fact that these medications are less effective at lowering triglyceride levels than fibrates, the evidence supporting an ASCVD benefit is tenuous as discussed above. Due to technical reasons, LDL cholesterol levels may be impossible to determine in a statin-treated patient with persistently elevated triglycerides. For these situations, non-HDL cholesterol and/or apo B are recommended as alternative laboratory tests to determine treatment thresholds and for monitoring the effects of therapy, according to the Canadian Lipid Guidelines.[19]

For the patient with severe hypertriglyceridemia and a history of acute pancreatitis, or an individual whose fasting triglyceride levels remain >10 mmol/L on repeated fasting lipid profiles without an obvious and treatable secondary cause, e.g., alcohol binge or decompensated diabetes, treatment is likely warranted to protect against pancreatitis. The first-line drug of choice in these cases should be a fibrate, with APOC3 inhibitors becoming a consideration in the near future for patients with persistent severe hypertriglyceridemia.

For those with a past history of hypertriglyceridemia-associated pancreatitis, who currently have only mild-to-moderate hypertriglyceridemia, an argument can still be

| Lifestyle |
|---|
| • Diet with high positive energy-intake balance and high fat or high glycemic index<br>• Obesity<br>• Physical inactivity<br>• Excess alcohol intake |
| **Medical Conditions** |
| • Metabolic syndrome<br>• Insulin resistance<br>• Diabetes mellitus (principally type 2)<br>• Metabolic dysfunction-associated steatotic liver disease (MASLD)<br>• Renal disease (proteinuria, uremia, or glomerulonephritis)<br>• Cushing syndrome<br>• Pregnancy (particularly third trimester)<br>• HIV infection<br>• Systemic lupus erythematosis<br>• Paraproteinemia<br>• Lipodystrophy |
| **Medications** |
| • Corticosteroids<br>• Oral estrogen<br>• Tamoxifen<br>• Thiazide diuretics<br>• Non-cardioselective beta-blockers<br>• Bile acid sequestrants<br>• Cyclophosphamide<br>• L-asparaginase<br>• Protease inhibitors<br>• Second generation antipsychotic agents (e.g. clozapine and olanzapine) |

**Table 1.** Secondary causes of hypertriglyceridemia; *courtesy of Robert A. Hegele, MD, FRCPC, Cert Endo, FACP*

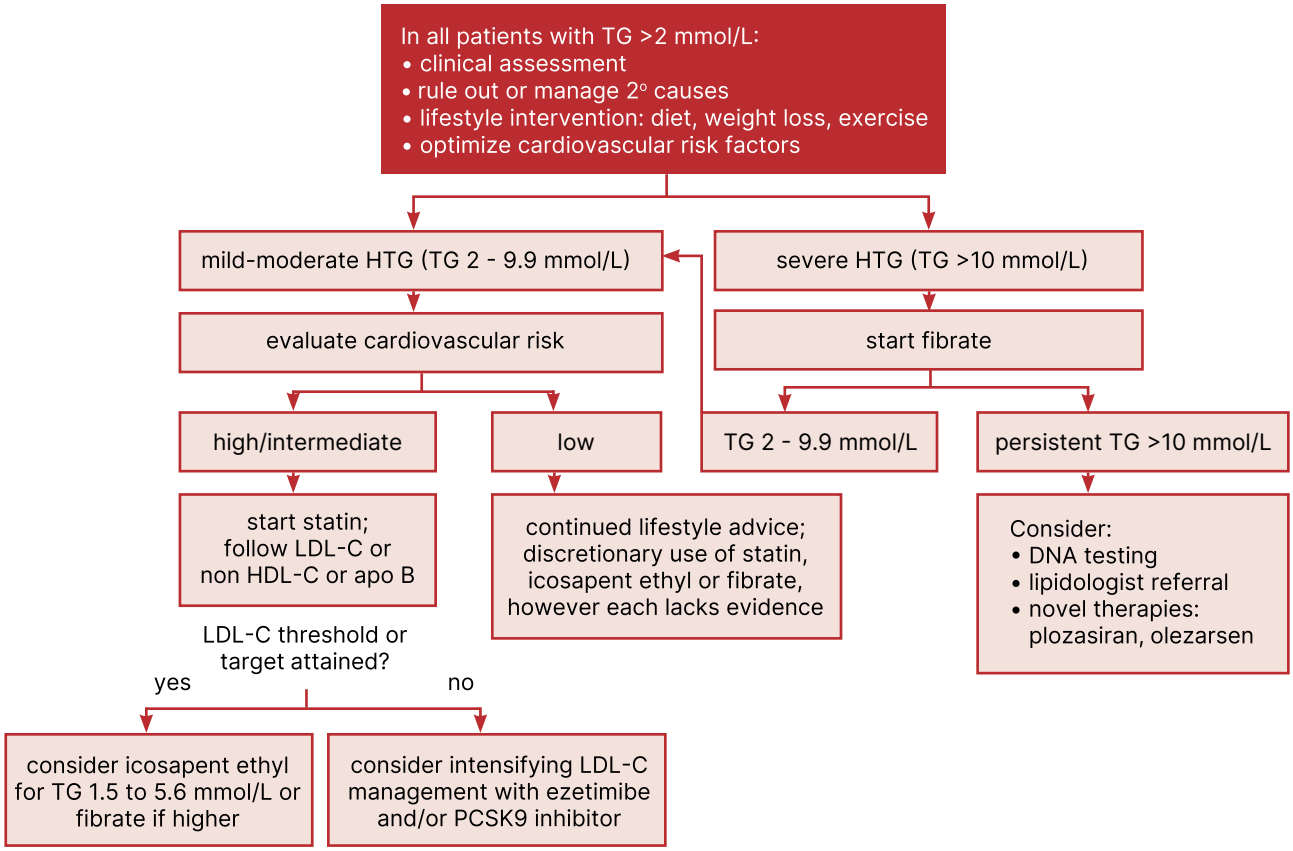


**Figure 1.** Approach to the patient with hypertriglyceridemia; *courtesy of Robert A. Hegele, MD, FRCPC, Cert Endo, FACP*

made for treatment with a fibrate to reduce the future risk of pancreatitis. Mild-to-moderate triglyceride elevation is also a predictor of future severe hypertriglyceridemia and the development of pancreatitis. Finally, for those at low cardiovascular risk with triglyceride levels below the pancreatitis threshold of 5 mmol/L, management of secondary contributors is the recommended course of action.[2,3]

## Conclusion

Hypertriglyceridemia is characterized by elevated serum triglyceride levels, with varying degrees of severity and associated risks. Severe hypertriglyceridemia (triglycerides >10 mmol/L) significantly increases the risk of acute pancreatitis, while mild-to-moderate hypertriglyceridemia (triglycerides 2 to 9.9 mmol/L) is associated with an increased cardiovascular disease risk. In all cases of hypertriglyceridemia, it is essential to manage the underlying secondary factors such as diabetes, obesity, and alcohol consumption. Treatment for severe hypertriglyceridemia focuses on reducing triglyceride levels to <5 mmol/L to prevent future episodes of acute pancreatitis. This is primarily accomplished by severe dietary fat restriction, the use of fibrates in some cases, and new biological therapies directed against APOC3, namely plozasiran and olezarsen. For mild-to-moderate hypertriglyceridemia, the primary goal is to reduce cardiovascular risk through lifestyle modifications and pharmacological interventions. These include weight loss, dietary modifications, regular physical activity, and limiting alcohol consumption. For patients with diabetes or established atherosclerotic cardiovascular disease, with mild-to-moderate hypertriglyceridemia on statin therapy, adding icosapent ethyl has been shown to reduce 3- and 5-point MACE as seen in the REDUCE-IT trial and recommended by the Canadian Lipid Guidelines.[19]

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# PCSK9 Targeted Therapy to Lower Cholesterol and Reduce Cardiovascular Events

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## Introduction

Cardiovascular disease (CVD) is an insidious threat that requires attention. Modifying risk factors can work toward preventing the current CVD epidemic.[1] Elevated low-density lipoprotein cholesterol (LDL-c) is a well-established and modifiable risk factor for cardiovascular, cerebrovascular, and peripheral vascular diseases. Despite receiving maximally tolerated doses of statin therapy, many Canadian patients with CVD do not achieve LDL-c targets.[2] Additional lipid-lowering therapies, such as ezetimibe or proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i), are warranted.[3]

This paper reviews the mechanisms of action and clinical trial evidence for contemporary lipid-lowering therapies, including PCSK9 inhibitor monoclonal antibodies such as evolocumab and alirocumab, and small interfering RNA (siRNA) modulators such as inclisiran, to aid Canadian clinicians in maintaining best practices.

## PCSK9 and Its Role in Lipid Metabolism

PCSK9 is secreted by hepatocytes, hindering low-density lipoprotein receptor (LDL-R) recycling and reducing LDL-R expression on the cells' surface. PCSK9 binds to the LDL-R on the hepatocytes' surface, resulting in a conformational change in the LDL-R such that it becomes trapped in the cell's endosome and cannot return to its surface. This process promotes LDL-R degradation and reduces its levels at the cell surface, leading to increased circulating LDL-c levels. Therefore, blocking PCSK9 prevents the degradation of the LDL-R, leading to increased LDL-R on the hepatocyte surface and enhanced LDL-c clearance, lowering LDL-c concentration.

Genetic studies have linked PCSK9 to individuals with hypercholesterolemia[4] and families with nonsense mutations to those with very low LDL levels.[5] These studies provided the impetus to use this protein as a therapeutic target to lower LDL-c in those with hypercholesterolemia or those with difficulties achieving therapeutic targets with traditional statin therapies.

## PCSK9 Monoclonal Antibodies: Alirocumab and Evolocumab

Alirocumab (Praluent) and evolocumab (Repatha) are monoclonal antibodies that bind to extracellular PCSK9, leading to reduced degradation of LDL-R and increasing their availability for LDL-c clearance.

### Clinical Efficacy

The efficacy and safety of alirocumab on LDL-c was initially assessed in the ODYSSEY LONG TERM trial, a randomized trial involving 2341 patients at high-risk for cardiovascular events with LDL-c levels >1.8 mmol/L despite receiving the maximally tolerated doses of statin therapy.[6] Patients were eligible if they were 18 years of age or older with heterozygous familial hypercholesterolemia or established coronary disease or its equivalent. The majority of patients were men, with an average age of 60, with 68.9% having a history of coronary heart disease. Some patients had familial hypercholesterolemia (17.7%). The baseline LDL-c level at entry was 3.2 mmol/L. Patients received either alirocumab 150 mg or placebo every 2 weeks for 78 weeks. By 24 weeks, the mean LDL-c level was reduced by −61.9%±1.3% ($p<0.001$) and was maintained for the duration of the 78 weeks of the study (−56.0%±1.6% reduction). The study drug resulted in more adverse side effects, including

injection site reactions (5.9% alirocumab vs 4.2% placebo), myalgias (5.4% alirocumab vs 2.9% placebo), neurocognitive events (1.2% alirocumab vs
0.5% placebo) and ophthalmologic events (2.9% alirocumab vs 1.9% placebo). A specific safety analysis of the larger ODYSSEY OUTCOMES trial demonstrated alirocumab's safety profile among higher-risk individuals[7] and did not confirm adverse side effects. Alirocumab was deemed safe except for a slight increase in the risk of injection site reactions.

The efficacy of evolocumab on LDL-c was assessed In the Durable Effect of PCSK9 Antibody Compared with Placebo Study (DESCARTES) in adult patients with LDL-c levels >1.94 mmol/L and fasting triglyceride levels <4.52 mmol/L. Patients were stratified to diet alone or diet plus lipid-lowering therapy baselines and then received either evolocumab or placebo. A total of 901 patients with hyperlipidemia received evolocumab over 1 year. The mean reduction in LDL-c from baseline was 57.0±2.1% (p<0.001).[8]

## Outcome Trials

The ODYSSEY OUTCOMES trial was a randomized, double-blind, trial involving 18,924 post-acute coronary syndrome (ACS) patients on evidence-based statin therapy, comparing the addition of alirocumab to placebo adequately powered for clinical outcomes.[9] The trial primarily enrolled white men with a history of hypertension following ACS, with 48% having NSTEMI or 34.9% having STEMI. The primary endpoint, a composite of death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, and unstable angina requiring hospitalization, was reduced in the alirocumab group (9.5%) vs the placebo group (11.1%), with a hazard ratio (HR) of 0.85 (95% confidence interval [CI] 0.78–0.93, p<0.001). The secondary end-points of death/myocardial infarction/ischemic stroke were reduced in the alirocumab group vs. placebo group (10.3% vs. 11.9%, p=0.0003), all-cause mortality was reduced (3.5% vs. 4.1%, p=0.026), and ischemia-driven revascularization was reduced (7.7% vs. 8.8%, p=0.009). There was an increase in mild, self-limiting injection site reactions of 3.8% in the alirocumab group vs 2.1% in placebo.

The Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) study was a randomized, double-blind, placebo-controlled trial of 27,564 patients comparing evolocumab to placebo in those 40-85 years of age with cardiovascular disease or at risk of cardiovascular disease with an LDL-c level >1.8 mmol/L while on statin therapy.[9] The majority of patients were male (75%) with a previous myocardial infarction (80.9%) on high-intensity statin therapy (69.5%) with a baseline LDL-c level of 2.38 mmol/L. Patients received subcutaneous injections of evolocumab 140 mg every 2 weeks or 420 mg subcutaneous every month, with the dose increased to 420 mg every 2 weeks if additional LDL-c lowering was required. The primary endpoint, which included a composite of cardiovascular death, myocardial infarction, stroke, and hospitalization for unstable angina or coronary revascularization, was reduced in patients in the evolocumab group compared to the control group (9.8% vs 11.3%; HR 0.85; 95% CI 0.79–0.92; p<0.001). The secondary endpoint, which included a composite of cardiovascular death, myocardial infarction or stroke, was also reduced in the evolocumab group compared to placebo (5.9% vs 7.4%, HR 0.80; 95% CI 0.73–0.88; p<0.001). There was an increase in mild injection-site-related reactions (2.1% in the evolocumab group vs 1.6% of those receiving placebo). There was a reduction in ischemic stroke in the evolocumab group vs the placebo group 1.2% versus 1.6% (HR 0.75; 95% CI 0.62–0.92; p=0.005).[10] Importantly, in the 13.2% of patients with peripheral arterial disease (PAD), there was a reduced risk of major adverse limb events (HR 0.58; 95% CI 0.38–0.88; p=0.0093),[11] highlighting the benefit of aggressive LDL lowering for these patients.[12]

In an open-label extension trial that followed patients for a median of 5 years, those treated with evolocumab experienced a 15% lower risk of cardiovascular death, myocardial infarction, stroke, or hospitalization for unstable angina or coronary revascularization (HR 0.85; 95% CI 0.75–0.96; p=0.008).[13] In addition, there was a 20% lower risk of CV death, myocardial infarction, or stroke (HR 0.80; 95% CI 0.68–0.93; p=0.003) and a 23% lower risk of cardiovascular death (HR 0.77; 95% CI 0.60–0.99; p=0.04). Compared with patients originally randomized to placebo, patients who received evolocumab had fewer cardiovascular events and lower cardiovascular mortality an important signal in the long-terms outcomes of PCSK9 inhibitor-treated patients.

### Indications For Use in Canada

Alirocumab was approved on July 31, 2019, for use in combination with the maximum tolerated dose of a statin to reduce the risk of myocardial infarction, ischemic stroke, and unstable angina requiring hospitalization in adults with established cardiovascular disease. It is also indicated to be used alone or with other lipid-lowering therapies in patients with heterozygous familial hypercholesterolemia.[14]

Evolocumab was approved in Canada on September 15, 2015, for the reduction of elevated LDL-c in adults with heterozygous familial hypercholesterolemia or ASCVD, with or without other lipid-lowering therapies in patients who require additional lowering of LDL-c, either alone or in combination with non-statin therapies for whom statins are contraindicated.[15]

## PCSK9 siRNA: Inclisiran

### Mechanism of Action

Inclisiran is a long-acting, small interfering RNA (siRNA) that selectively silences the translation of PCSK9 mRNA in the liver to reduce the production of PCSK9 protein. This results in an increased availability of the LDL-R on hepatocytes, leading to increased clearance of LDL-c. Due to its mechanism of action interfering with mRNA production of PCSK9 in the liver, inclisiran can be given every 6 months subcutaneously after the initial dose and 3-month second dose.

### Clinical Efficacy

The ORION-9 (Trial to Evaluate the Effect of Inclisiran Treatment on Low-Density Lipoprotein Cholesterol in Subjects With Heterozygous Familial Hypercholesterolemia and Atherosclerotic Cardiovascular Disease), ORION-10 (Inclisiran for Participants With Atherosclerotic Cardiovascular Disease and Elevated Low-density Lipoprotein Cholesterol), and ORION-11 (Inclisiran for Subjects

| Study Drug | Mechanism of Action | LDL-c Lowering | Clinical Efficacy |
|---|---|---|---|
| Alirocumab | Antibody to PCSK9 | −61.9±1.3% | **Patients studied:** Post-acute coronary syndrome patients on maximally tolerated statin therapy.<br><br>**Outcome:** Reduction in a composite of coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, and unstable angina requiring hospitalization. |
| Evolocumab | Antibody to PCSK9 | −57.0±2.1% | **Patients studied:** Patients with cardiovascular disease or at risk with an LDLc level >1.8 mmol/L on maximally tolerated statin therapy.<br><br>**Outcome:** Reduction in a composite of cardiovascular death, myocardial infarction, stroke, and hospitalization for unstable angina or coronary revascularization. |
| Incilisiran | siRNA to PSCK9 | ORION- 9: −47.9%±5.6%<br>ORION-10: −53.8%±2.8%<br>ORION-11: 49.2%±2.4% | Pending Ongoing CVO trials, – Pooled analysis is encouraging |

**Table 1.** PCSK9 targeted therapies, efficacy and indications.; *courtesy of Beth L. Abramson, MD, FRCPC, FACC, Seana ML. Nelson, MD, FRCPC*

**Abbreviations: ASCVD:** atherosclerotic cardiovascular disease; **CVO:** cardiovascular outcome trials; **LDL-c:** low-density lipoprotein cholesterol; **PCSK9:** proprotein convertase subtilisin/kexin type 9

With ASCVD or ASCVD-Risk Equivalents and Elevated Low-density Lipoprotein Cholesterol) studies investigated the LDL-c lowering capabilities of inclisiran. These trials demonstrated an approximate 50.3% reduction in LDL-c levels.[16,17] Injection site reactions were more frequent in the study group, and most of them were mild.

The ORION-9 study included individuals with familial hypercholesterolemia who had LDL-c levels >2.6 mmol/L despite receiving maximally tolerated statin therapy with or without ezetimibe.[16] Patients were randomized to receive either inclisiran 284 mg or placebo. The primary endpoints included the percentage change in LDL-c levels from baseline to day 510. In the inclisiran group, LDL-c levels were reduced by 39.7% (95% CI −43.7 to −35.7) and were increased by 8.2% (95% CI 4.3–12.2) in the placebo group, resulting in a net change of −47.9 percentage points (95% CI −53.5 to −42.3; p<0.001). Other outcomes included lower levels of total cholesterol, non-HDL, apolipoprotein B, and triglycerides compared to the placebo group. In addition, lipoprotein (a) was reduced by 17.2% compared to baseline.

The ORION-10 study included patients in the US with atherosclerotic cardiovascular disease and LDL-c levels >1.8 mmol/L on a background of lipid-lowering therapies.[17] The ORION-11 study included individuals from South Africa and Europe with atherosclerotic cardiovascular disease and LDL-c levels >1.8 mmol/L? or an atherosclerotic disease equivalent.[17] Individuals received either inclisiran 284 mg or placebo. In the ORION-10 study, the coprimary endpoints included the percentage LDL-c change, which was 1% in the placebo group and 51.3% in the inclisiran group, resulting in an absolute inter-group change of -53.8% (95%CI −55.7 to −48.8; p<0.001). In the ORION-11 study, LDL-c levels increased by 4% in the placebo group and decreased by 45.8% in the inclisiran group, leading to an in-between difference of -49% (95% CI −53.1 to −46.6; p<0.001).

The ORION-3 trial, a 4-year open-label extension study of 382 patients previously enrolled in the ORION-1 study, demonstrated the safety and efficacy of inclisiran.[18] Patients who received inclisiran in the ORION-1 trial received 284 mg biannually. Those randomized to the placebo group in the ORION-1 trial received 140 mg of evolocumab subcutaneously and then transitioned to 284 mg of inclisiran after 1 year for the remainder of the study. The mean percentage reduction in LDL-c levels ranged from −34·3% to −53·8%, and the mean absolute change in LDL-c concentrations ranged from−1·13 mmol/L to −1·76 mmol/L. The most common treatment-related event was nasopharyngitis in the inclisiran-only group (19%) and hypertension (20%) in the switching group. Between 25-28% of patients in the study experienced injection site-related reactions.

### Outcome Data

The effect of inclisiran on cardiovascular morbidity and mortality has not been assessed in a specific trial, but pooled data from the three Phase III trials is encouraging.[19] The ORION-4 trial, which has enrolled 16,124 participants with pre-existing atherosclerotic disease, aims to determine if inclisiran can reduce major cardiac events [ClinicalTrials.gov Identifier: NCT03705234] and expects to report findings in 2026. The VICTORION-1P and 2P trials will assess the efficacy of inclisiran in approximately 15,000 patients who are either at high risk for primary prevention or have established cardiovascular disease. The findings are expected to be reported in 2029 and 2027, respectively.

### Indications For Use In Canada

Inclisiran (Leqvio) was approved in Canada on July 23, 2021, to further reduce LDL-c levels in adults on maximally tolerated statin therapy who have heterozygous familial hypercholesterolemia or non-familial hypercholesterolemia with atherosclerotic cardiovascular disease.[20]

## Conclusions

PCSK9 plays an important role in handling LDL-R and, therefore, circulating LDL-c. Mendelian studies have demonstrated a correlation between PCSK9 overexpression and increased cardiovascular disease, while nonsense mutations are associated with a lower cardiovascular risk.

The Canadian Cardiology Society 2021 Dyslipidemia Guidelines endorse PSCK9i for familial and ASCVD patients. In those with familial hypercholesterolemia (FH) or genetic dyslipidemia, PSCK9i is indicated if LDL >2.5, ApoB >0.85, or non-HDL-c >3.2. For ASCVD patients with LDL-c >2.2 mmol/L, non-HDL-c >2.9 mmol/L, or ApoB >0.8 g/L despite max statin therapy, PSCK9i is recommended as an add-on, especially for high PSCK9i benefit patients, including those with acute coronary syndrome (ACS) in the past year or additional risk factors like recurrent ACS, past CABG, poly-vascular disease, symptomatic PAD,

high LDL-c, heterozygous FH, elevated Lp(a), or diabetes. If ASCVD patients don't meet these criteria but have LDL-c >1.8 mmol/L, ApoB >0.7 g/L, or non-HDL >2.4 on maximum statin therapy, ezetimibe is added first, with PSCK9i considered later. Both PCSK9 inhibitors, evolocumab and alirocumab, reduced cardiovascular and stroke events. In addition, PCSK9 modulation with inclisiran also effectively lowers LDL-c, with cardiovascular outcome trial data pending. Overall, PCSK9 targeted therapies provide therapeutic options to lower LDL-c to levels that were not possible several decades ago. Intensification of lipid-lowering in our at-risk patients will help reduce the tremendous burden cardiovascular disease places on our healthcare system and improve the health of our patients.[21]

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# Use of Antiplatelet Agents in Canadian Patients: A Reflection of the 2023 Antiplatelet Guidelines

**Guillaume Marquis-Gravel, MD, MSc**

## Introduction

Antiplatelet agents play a fundamental role in secondary prevention of atherosclerotic cardiovascular disease by reducing the risk of recurrent ischemic events. Over the past decades, developments and refinements in antiplatelet therapy have been made through the commercialization of novel classes (P2Y12 inhibitors, glycoprotein [GP] IIb/IIIa inhibitors), modes of administration (oral and intravenous), and combination strategies (dual antiplatelet therapy [DAPT] of different durations).[1] Recently, concerns have been raised regarding the prognostic impact of bleeding events associated with antiplatelet agents.[2] Consequently, multiple strategies have been studied to optimize the fine balance between ischemic protection and bleeding avoidance with these agents. The 2023 Focused Update of the Guidelines for the Use of Antiplatelet Therapy by the Canadian Cardiovascular Society/ Canadian Association of Interventional Cardiology distilled the most recent evidence on this topic from a Canadian perspective.[3] This review offers insights into the implementation of the guidelines' recommendations in routine clinical practice within the Canadian setting.

## Pre-treatment with DAPT Before Coronary Angiography

Patients undergoing percutaneous coronary intervention (PCI) with stent implantation require a combination of acetylsalicylic acid (ASA) and a P2Y12 receptor inhibitor (clopidogrel, ticagrelor, or prasugrel) to inhibit platelet function and prevent stent thrombosis. In theory, obtaining full platelet inhibition at the time of PCI requires administering a P2Y12 receptor inhibitor before the procedure (pre-treatment). However, it is often unknown beforehand if a PCI will be performed at the time of a coronary angiography, therefore pre-treating every patient with a P2Y12 inhibitor leads to unnecessary treatment for many, with an associated risk of bleeding. The new Canadian guidelines provide recommendations regarding pre-treatment for 3 indications of coronary angiography: ST-elevation myocardial infarction

(STEMI), Non-ST-elevation acute coronary syndrome (NSTE-ACS), and stable ischemic heart disease.[3] Routine pre-treatment is suggested for patients with STEMI, and for those with NSTE-ACS with the intent to perform coronary angiography >24 hours after admission (weak recommendation, low-quality evidence). However, pre-treatment is not recommended for those with NSTE-ACS with the intent to perform coronary angiography within <24 hours (weak recommendation, moderate-quality evidence) or for elective patients (weak recommendation, low-quality evidence). For all patients, however, ASA needs to be administered before the procedure and continued afterwards if PCI is performed. A meta-analysis conducted during the development of the guidelines showed that pre-treatment for NSTE-ACS does not reduce the risk of ischemic events (mortality, major adverse cardiac and cerebrovascular events [MACE], and stent thrombosis), but it does increase the risk of major bleeding. The largest study on this topic, the ACCOAST trial, randomized 4,033 participants with non-ST-elevation myocardial infarction (NSTEMI) to receive either prasugrel pre-treatment, or prasugrel at the time of PCI.[4] Pre-treatment increased the risk of major bleeding (2.6% versus 1.4%, p=0.006), without reducing MACE at 7 days (10.0% versus 9.8%, p=0.81). However, the procedure was performed within 24 hours after admission in the ACCOAST trial, similar to most trials in the meta-analysis, except for the Canadian CURE trial.[5] In the Canadian context, PCI is often performed >24 hours after diagnosis of NSTE-ACS. During the waiting period, these patients are at risk of thrombotic complications, which justifies the discrepant recommendations for NSTE-ACS based on the timing of the procedure. Cangrelor, an intravenous P2Y12 inhibitor with rapid onset and offset of action, recently received Health Canada approval to decrease the risk of thrombotic cardiovascular events in patients undergoing PCI who have not received an oral P2Y12 inhibitor or other intravenous antiplatelet agents. Its role remains to be defined in the Canadian context, and it may be addressed in future iterations of the Canadian guidelines.

## DAPT for ACS and PCI

Clopidogrel no longer represents the P2Y12 inhibitor of choice for patients admitted to the hospital with an acute coronary syndrome (ACS). Instead, the more potent prasugrel or ticagrelor are recommended as part of DAPT in combination with ASA. Both agents are superior to clopidogrel to prevent recurrent ischemic events, however, there is insufficient head-to-head evidence to support one superior agent over the other. Therefore, neither prasugrel nor ticagrelor is preferred over the other for patients with ACS undergoing PCI (weak recommendation, low-quality evidence). Ticagrelor is more widely available across Canadian provinces than prasugrel. However, it is associated with a 13%-31% rate of dyspnea, leading to drug discontinuation in 1%-7% of patients.[6] It is also administered twice daily, while prasugrel is administered once daily. When contemplating switching from ticagrelor due to side effects, prasugrel should be considered in the right context.

To reduce the risk of major bleeding, without compromising the risk of major adverse cardiovascular events, switching from prasugrel/ticagrelor to clopidogrel after one month is a reasonable alternative based on the TOPIC and TALOS-AMI trials (weak recommendation, moderate-quality evidence).[7,8] Indeed, the risk of recurrent ischemic events is the highest during the first month, and decreases thereafter, making clopidogrel a suitable option. In the TALOS-AMI trial, 2,697 patients with ACS who underwent PCI and were on DAPT with ticagrelor were randomized at 30 days to either continue ticagrelor or to switch from ticagrelor to clopidogrel.[7] The primary endpoint, a composite of cardiovascular death, myocardial infarction, stroke, or bleeding type 2, 3, or 5, according to the Bleeding Academic Research Consortium (BARC) criteria from 1 to 12 months, occurred in 4.6% of participants in the clopidogrel group, and 8.2% of participants in the ticagrelor group (p for superiority=0.0001). There was no significant difference in the risk of cardiovascular death, myocardial infarction, or stroke, between the groups. However, there was a significant reduction in bleeding events with clopidogrel. Of note, patients at high bleeding risk were excluded from the TALOS-AMI trial, suggesting that clopidogrel de-escalation is a suitable strategy that should be considered for all patients, not exclusively those at high bleeding risk. The available evidence is currently not sufficient to recommend dose de-escalations of prasugrel/ticagrelor as part of DAPT to minimize bleeding risk, and therefore no recommendations were issued in the guidelines on this topic.

More recently, studies evaluated the role of ultra-short DAPT durations after PCI (<1 month, and as low as only one day), followed by P2Y12 inhibitor monotherapy (ASA-free strategy).[9,10] This strategy still requires validation before implementation into routine clinical practice, and is currently not recommended.

Patients at high bleeding risk (HBR) represent a particularly challenging population, given that bleeding risk factors often coincide with ischemic risk factors, complexifying decisions about DAPT. A standardized definition of high bleeding risk has been developed by the Academic Research Consortium that can be used in clinical practice to identify these patients **(Table 1)**.[11] This vulnerable subgroup has historically been excluded from randomized controlled trials evaluating DAPT strategies after PCI, contributing

| Major Criteria | Minor Criteria |
|---|---|
| End-stage CKD with eGFR <30 mL/min | CKD with eGFR 30-59 mL/min |
| Hemoglobin <110 g/L | Hemoglobin 110-129 g/L for men and 110-119 g/L for women |
| Spontaneous bleeding requiring hospitalization or transfusion within the past 6 months (or at any time, if recurrent) | Spontaneous bleeding requiring hospitalization or transfusion within the past 12 months not meeting the major criterion |
| • Previous spontaneous ICH (at any time)<br>• Previous traumatic ICH within the past 12 months<br>• Presence of a brain arteriovenous malformation<br>• Moderate or severe ischemic stroke within the past 6 months | Any ischemic stroke at any time not meeting the major criterion |
| Moderate or severe baseline thrombocytopenia (platelet count <100×10$^9$/L) | Long-term use of oral NSAIDs or steroids |
| Anticipated use of long-term OAC | Age ≥75 years |
| Chronic bleeding diathesis | |
| Liver cirrhosis with portal hypertension | |
| Active malignancy within the past 12 months (excluding nonmelanoma skin cancer) | |
| Nondeferrable major surgery on DAPT | |
| Recent major surgery or major trauma within 30 days before PCI | |

**Table 1.** Academic Research Consortium (ARC) High Bleeding Risk (HBR) Criteria in Patients Undergoing PCI; *courtesy of Guillaume Marquis-Gravel, MD, MSc*

**Abbreviations: CKD:** chronic kidney disease; **eGFR:** estimated glomerular filtration rate; **DAPT:** dual antiplatelet therapy; **ICH:** intracranial hemorrhage; **NSAID:** nonsteroidal anti-inflammatory drug; **OAC:** oral anticoagulation; **PCI:** percutaneous coronary intervention

to uncertainty in terms of the safest and more effective approach. More recently, however, the MASTER DAPT trial exclusively enrolled patients considered to be at high bleeding risk after PCI.[12] The 4,434 participants were randomized to either discontinue DAPT after one month, or continue DAPT for at least 5 additional months (for those without concomitant oral anticoagulation [OAC]). The abbreviated DAPT strategy decreased the risk of bleeding without compromising ischemic endpoints. On this basis, the guidelines recommend a 1-3 month DAPT duration (instead of 6-12 months) after PCI for patients at high bleeding risk (weak recommendation, moderate-quality evidence).

## Antiplatelet Therapy for Patients with PCI and Atrial Fibrillation Requiring OAC

Patients with atrial fibrillation and an indication of chronic OAC are at a higher risk of bleeding complications with antiplatelet therapy after PCI or myocardial infarction. The AUGUSTUS factorial randomized controlled trial is the only trial which specifically evaluated the role of ASA in these patients, regardless of the type of OAC used.[13] Among the 4,614 participants treated with a P2Y12 inhibitor and an OAC, major or clinically relevant nonmajor bleeding occurred in 16.1% of patients treated with ASA, and in 9.0% of those treated with placebo (p<0.001). The incidence rates of death, hospitalization, and ischemic events were similar between both groups. A meta-analysis conducted during the development of the guidelines, which included 11,156 participants from 6 randomized controlled trials, suggested that dual therapy with OAC + a P2Y12 inhibitor (without ASA) was associated with 23 fewer major bleeding events per 1,000 patients versus triple therapy (OAC + P2Y12 inhibitor + ASA). However, it was associated with 8 more MACE per 1,000 patients. Therefore, in light of the net clinical benefits of dual therapy, it is recommended to stop ASA within 1-30 days after PCI or ACS in patients treated with a P2Y12 inhibitor and concomitant OAC (weak recommendation, moderate-quality evidence). Of note, at the time of PCI, all patients should be treated with ASA, which can be stopped thereafter. The optimal timing for stopping ASA remains unknown. However, in the trials included in the meta-analysis, it was stopped on average between 1.6 to 6.6 days after the index event. Therefore, it is generally reasonable to consider stopping ASA at the time of discharge. Clopidogrel is the most extensively studied P2Y12 inhibitor when used in combination with an OAC and should be preferred for these patients given the uncertainty regarding the safety of ticagrelor and prasugrel in this context. After 12 months, OAC can be continued as a monotherapy, without any antiplatelet agent (weak recommendation, very low-quality evidence), based on the AFIRE randomized controlled trial.[14] In this trial that included 2,236 patients with atrial fibrillation who underwent coronary revascularization >1 year before, OAC monotherapy with rivaroxaban was found to be non-inferior to OAC + single antiplatelet therapy regarding the primary endpoint, which was a composite of stroke, systemic embolism, myocardial infarction, unstable angina requiring revascularization, or death from any cause, which occurred at rates of 4.14% versus 5.75%, respectively; p<0.001 for non-inferiority). OAC monotherapy was also associated with a significant reduction in major bleeding (1.62% versus 2.76%; p=0.01) and all-cause mortality (1.85% versus 3.37%).

## ASA for Primary Prevention of Atherosclerotic Cardiovascular Disease

ASA has long been used to prevent atherosclerotic cardiovascular thrombotic events in high-risk patients without established atherosclerotic cardiovascular disease, such as elderly patients and those with diabetes. However, it is no longer recommended routinely in primary prevention, regardless of sex, age, or diabetes (strong recommendation, high-quality evidence).[3] This new recommendation is based on a meta-analysis of 167,587 participants from 14 randomized controlled trials, which showed that while ASA reduces major adverse cardiovascular events in this context, the absolute reduction is low (4 fewer events per 1,000 patients over 5 years). However, this benefit is accompanied by a similar increase in extracranial major bleeding events (5 additional events per 1,000 patients over 5 years). In this context, the net benefits of ASA for primary prevention are neutral. However, the guidelines endorse a patient-centred, informed, shared decision-making process, in which some patients who strongly prefer ischemic risk reduction over bleeding risk avoidance may be considered for ASA in primary prevention. The guidelines include a “Primary Prevention Decision Aid Tool” to support physicians and ensure their patients make the best decision for their specific context.

## KeyTake-home Messages

1. Routine pre-treatment with a P2Y12 inhibitor is not recommended for patients undergoing elective coronary angiography or those with a NSTE-ACS who have a procedure planned <24 hours after hospital admission. However, routine pre-treatment is suggested for patients with STEMI or with NSTE-ACS who have a procedure planned >24 hours, which is common in the Canadian context.
2. Prasugrel or ticagrelor are preferred over clopidogrel for patients with ACS treated with PCI to reduce ischemic events, and de-escalating to clopidogrel at 1 month can be considered to reduce bleeding.
3. For patients at high bleeding risk undergoing PCI, an abbreviated DAPT duration (typically 1-3 months) can be considered because it reduces bleeding without compromising ischemic safety.
4. For patients with ACS and/or PCI requiring a concomitant OAC for atrial fibrillation, a dual pathway strategy (P2Y12 inhibitor + OAC) is preferred over triple therapy (P2Y12 inhibitor + OAC + ASA) 1-30 days after the index event. After 12 months, OAC can be continued as monotherapy.
5. ASA is not routinely recommended for primary prevention, but the decision to use it should be based on a patient-centred, informed, and shared decision-making process with the patient.

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## Financial Disclosures

**G.M-G.:** None declared.

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